

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION
 (PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 July 2001 (13.07.01)	To:
International application No. PCT/EP00/09149	Applicant's or agent's file reference 0480/001219
International filing date (day/month/year) 19 September 2000 (19.09.00)	Priority date (day/month/year) 24 September 1999 (24.09.99)
Applicant HANTKE, Thomas et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

23 April 2001 (23.04.01)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer A. Karkachi
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 13 July 2001 (13.07.01)	To: KINZEBACH, Werner Ludwigsplatz 4 67059 Ludwigshafen ALLEMAGNE												
Applicant's or agent's file reference 0480/001219	IMPORTANT NOTIFICATION												
International application No. PCT/EP00/09149	International filing date (day/month/year) 19 September 2000 (19.09.00)												
<p>1. The following indications appeared on record concerning:</p> <p><input type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input checked="" type="checkbox"/> the agent <input type="checkbox"/> the common representative</p> <table border="1"> <tr> <td>Name and Address GOLDSCHEID, Bettina BASF Aktiengesellschaft 67056 Ludwigshafen Germany</td> <td>State of Nationality</td> <td>State of Residence</td> </tr> <tr> <td></td> <td>Telephone No.</td> <td>0621/60-78916</td> </tr> <tr> <td></td> <td>Facsimile No.</td> <td>0621/60-43123</td> </tr> <tr> <td></td> <td>Teleprinter No.</td> <td></td> </tr> </table>		Name and Address GOLDSCHEID, Bettina BASF Aktiengesellschaft 67056 Ludwigshafen Germany	State of Nationality	State of Residence		Telephone No.	0621/60-78916		Facsimile No.	0621/60-43123		Teleprinter No.	
Name and Address GOLDSCHEID, Bettina BASF Aktiengesellschaft 67056 Ludwigshafen Germany	State of Nationality	State of Residence											
	Telephone No.	0621/60-78916											
	Facsimile No.	0621/60-43123											
	Teleprinter No.												
<p>2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:</p> <p><input checked="" type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence</p> <table border="1"> <tr> <td>Name and Address KINZEBACH, Werner Ludwigsplatz 4 67059 Ludwigshafen Germany</td> <td>State of Nationality</td> <td>State of Residence</td> </tr> <tr> <td></td> <td>Telephone No.</td> <td>0621/591390</td> </tr> <tr> <td></td> <td>Facsimile No.</td> <td>0621/628441</td> </tr> <tr> <td></td> <td>Teleprinter No.</td> <td></td> </tr> </table>		Name and Address KINZEBACH, Werner Ludwigsplatz 4 67059 Ludwigshafen Germany	State of Nationality	State of Residence		Telephone No.	0621/591390		Facsimile No.	0621/628441		Teleprinter No.	
Name and Address KINZEBACH, Werner Ludwigsplatz 4 67059 Ludwigshafen Germany	State of Nationality	State of Residence											
	Telephone No.	0621/591390											
	Facsimile No.	0621/628441											
	Teleprinter No.												
<p>3. Further observations, if necessary:</p>													
<p>4. A copy of this notification has been sent to:</p> <table> <tr> <td><input checked="" type="checkbox"/> the receiving Office</td> <td><input type="checkbox"/> the designated Offices concerned</td> </tr> <tr> <td><input type="checkbox"/> the International Searching Authority</td> <td><input checked="" type="checkbox"/> the elected Offices concerned</td> </tr> <tr> <td><input checked="" type="checkbox"/> the International Preliminary Examining Authority</td> <td><input type="checkbox"/> other:</td> </tr> </table>		<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned	<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned	<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:						
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned												
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned												
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:												

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer A. Karkachi Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

KINZEBACH, Werner
Ludwigsplatz 4
67059 Ludwigshafen
ALLEMAGNE

Date of mailing (day/month/year) 11 April 2002 (11.04.02)	
Applicant's or agent's file reference M42109-PCT	IMPORTANT NOTIFICATION
International application No. PCT/EP00/09149	International filing date (day/month/year) 19 September 2000 (19.09.00)

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address KNOLL AKTIENGESELLSCHAFT 67061 Ludwigshafen Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address ABBOTT GMBH & CO. KG Max-Planck-Ring 2 D-65205 Wiesbaden Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Lazar Joseph PANAKAL Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 10 April 2002 (10.04.02)	From the INTERNATIONAL BUREAU To:
--------------------------------------------------------------	--------------------------------------

KINZEBACH, Werner
Ludwigsplatz 4
67059 Ludwigshafen
ALLEMAGNE

Applicant's or agent's file reference 0480/001219	IMPORTANT NOTIFICATION
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International application No. PCT/EP00/09149	International filing date (day/month/year) 19 September 2000 (19.09.00)
-------------------------------------------------	----------------------------------------------------------------------------

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address KNOLL AKTIENGESELLSCHAFT 67061 Ludwigshafen Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
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Name and Address ABBOTT GmbH & Co. KG Max-Planck-Ring 2 D-65205 Wiesbaden Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

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<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Lazar Joseph PANAKAL Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0480/001219	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/09149	International filing date (day/month/year) 19/09/2000	Priority date (day/month/year) 24/09/1999	
International Patent Classification (IPC) or national classification and IPC C07D239/48			
Applicant KNOLL AKTIENGESELLSCHAFT et al.			

<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 1 sheets.</p>
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand 23/04/2001	Date of completion of this report 11.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Beeck, M Telephone No. +49 89 2399 8473





**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09149

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-15 as originally filed

Claims, No.:

1 (part).6-15 as originally filed

1 (part).2-5 as received on 21/11/2001 with letter of 21/11/2001

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - the language of publication of the international application (under Rule 48.3(b)).
 - the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
 - the claims, Nos.:
 - the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09149

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-15
	No: Claims
Inventive step (IS)	Yes: Claims 1-15
	No: Claims

Industrial applicability (IA)	Yes: Claims 1-15
	No: Claims

2. Citations and explanations **see separate sheet**

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09149

SECTION V:

- 1) The documents are numbered according to their sequence in the search report.
- 2) Document D5 discloses in example 39, column 37, (b) Tablet II, a tablet comprising a 4,6-dianilino-pyrimidine derivative of formula (I), falling under the general formula of present claim 1, and polyvinylpyrrolidone.

Documents D6 and D7 describe substituted 2-anilinopyrimidines, falling under the general formula of present claim 1, with polyvinylpyrrolidone as binding agent (see D6, page 15, line 17, and D7, page 17, line 11).

Document D8 also describes diaminopyrimidine derivatives, falling under the general formula of present claim 1, with polyvinylpyrrolidone as carrier (see page 9, line 21).

P-document D9 has a filing date of 24.3.99, which is before the priority date of the present application, and describes triazine derivatives falling under the general formula of present claim 1, in combination with polyvinylpyrrolidone (see example D1 on page 32).

Also P-document D11 has a filing date before the priority date of the present application. D11 discloses in example D1 on page 30 a formulation of compounds which fall under the general formula of present claim 1 and which contain polyvinylpyrrolidone.

The subject-matter of the claims differs from these documents in that the compounds constitute a **solid solution** in the polymeric matrix.

Therefore the subject-matter of the claims is novel.

It also involves an inventive step, since solid solutions of the compounds are not obvious for the person skilled in the art.

In addition, table 2 of the application shows the high dissolution rate of the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09149

compositions of the invention.

SECTION VI:

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 00 27828	18.5.00	4.11.99	10.11.99

SECTION VII:

The description has not yet been adapted to the wording of new claim 1.



Rec'd on 19 May 02

REPLACED BY

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- Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁₋₆alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; oxadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino;
- arylis phenyl or phenyl substituted with C₁₋₆alkyl or halo, and the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom,
- as a solid dispersion in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone.
- 35 2. Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.
3. Particles according to claim 1 or 2, further comprising a surfactant.
- 40 4. Particles according to claim 3, wherein the surfactant is a PEG-n-hydrogenated castor oil.
5. Particles according to any of the claims 1 to 3, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0480/001219	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/09149	International filing date (<i>day/month/year</i>) 19/09/2000	(Earliest) Priority Date (<i>day/month/year</i>) 24/09/1999
Applicant KNOLL AKTIENGESELLSCHAFT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
 - b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
2. Certain claims were found unsearchable (See Box I).
3. Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

 None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/09149

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07D239/48	C07D231/18	C07D239/50	C07D403/12	C07D521/00
	C07D405/14	A61K31/505	A61P35/00	A61K9/16	A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 872 233 A (JANSSEN) 21 October 1998 (1998-10-21) page 1 -page 11 ----	1-5, 10-12, 14,15
Y	EP 0 834 507 A (JANSSEN) 8 April 1998 (1998-04-08) cited in the application page 1 -page 5; claims; tables 2-5 ----	1-5, 10-12, 14,15
Y	WO 99 02523 A (JANSSEN) 21 January 1999 (1999-01-21) cited in the application the whole document ----	1-5, 10-12, 14,15

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

17 May 2001

Date of mailing of the international search report

31/05/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/09149

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 13499 A (JANSSEN) 9 May 1996 (1996-05-09) cited in the application page 0; claims; tables 10,11 ---	1-5, 10-12, 14,15
Y	US 5 880 130 A (ANDREW PETER THOMAS) 9 March 1999 (1999-03-09) column 37, line 10 -column 50 ---	1-5, 10-12, 14,15
Y	WO 97 19065 A (CELLTECH) 29 May 1997 (1997-05-29) page 1 -page 15; claims ---	1-5, 10-12, 14,15
Y	WO 98 41512 A (CELLTECH) 24 September 1998 (1998-09-24) page 1 -page 18; claims ---	1-5, 10-12, 14,15
Y	WO 91 18887 A (SMITH-KLINE) 12 December 1991 (1991-12-12) page 1 -page 10; claims ---	1-5, 10-12, 14,15
P,Y	WO 99 50256 A (JANSSEN) 7 October 1999 (1999-10-07) the whole document ---	1-5, 10-12, 14,15
P,Y	WO 00 27828 A (JANSSEN) 18 May 2000 (2000-05-18) cited in the application page 15; claims ---	1-5, 10-12, 14,15
P,Y	EP 0 945 443 A (JANSSEN) 29 September 1999 (1999-09-29) the whole document -----	1-5, 10-12, 14,15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/09149

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 872233	A	21-10-1998	NONE	
EP 834507	A	08-04-1998	AU 3926697 A BR 9704937 A CA 2216486 A CN 1180698 A CZ 9702993 A HR 970526 A HU 9701596 A JP 10114759 A NO 974368 A PL 322369 A SG 53075 A SK 131997 A TR 9701070 A TW 411335 B ZA 9708766 A	09-04-1998 06-06-2000 01-04-1998 06-05-1998 11-11-1998 31-10-1998 28-06-1999 06-05-1998 02-04-1998 14-04-1998 28-09-1998 11-06-1999 21-04-1998 11-11-2000 30-03-1999
WO 9902523	A	21-01-1999	AU 8857598 A AU 8857698 A BG 103934 A BR 9811676 A BR 9811679 A CN 1262675 T CN 1262684 T WO 9902496 A EP 1000029 A EP 1068200 A HR 20000004 A HR 20000007 A HU 0003078 A JP 2000515560 T NO 20000093 A PL 337648 A SK 182999 A SK 184199 A TR 200000020 T	08-02-1999 08-02-1999 30-11-2000 19-09-2000 19-09-2000 09-08-2000 09-08-2000 21-01-1999 17-05-2000 17-01-2001 31-12-2000 31-12-2000 29-01-2001 21-11-2000 10-03-2000 28-08-2000 14-08-2000 11-07-2000 21-09-2000
WO 9613499	A	09-05-1996	AP 779 A AT 198889 T AU 697744 B AU 3868095 A BG 101402 A BR 9509436 A CZ 9701198 A DE 69519995 D EP 0788496 A FI 971784 A HR 950532 A HU 77360 A IL 115771 A JP 3025907 B JP 9511759 T KR 227231 B NO 971895 A NZ 295353 A PL 319905 A RU 2144032 C	03-11-1999 15-02-2001 15-10-1998 23-05-1996 31-10-1997 06-01-1998 18-03-1998 01-03-2001 13-08-1997 25-04-1997 31-08-1997 30-03-1998 29-02-2000 27-03-2000 25-11-1997 01-11-1999 24-04-1997 26-08-1998 01-09-1997 10-01-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/09149

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9613499 A		SK 50797 A TR 960337 A US 5521186 A US 5929075 A ZA 9509084 A	08-04-1998 21-06-1996 28-05-1996 27-07-1999 29-04-1997
US 5880130 A	09-03-1999	AU 1194895 A EP 0733045 A WO 9515952 A JP 9506363 T ZA 9409546 A	27-06-1995 25-09-1996 15-06-1995 24-06-1997 23-06-1995
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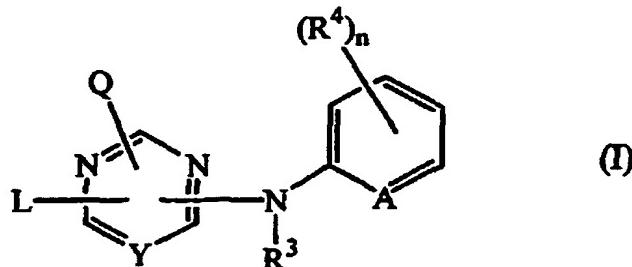
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(54) Title: RATE-CONTROLLED PARTICLES



(57) Abstract: Rate-controlled particles, comprising compounds of formula (I) as a solid dispersion.



Rate-controlled particles

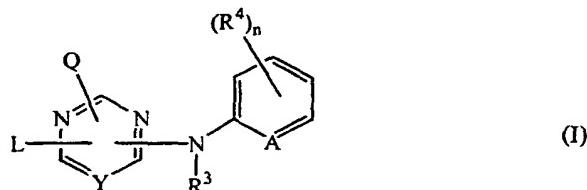
Specification

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The present invention concerns pharmaceutical compositions in the form of rate-controlled particles, comprising compounds of the formula (I) to (VI)

10 (I) is an antiviral compound of formula

15



a N-oxide, a pharmaceutically acceptable addition salt or a
20 stereochemically isomeric form thereof, wherein

- Y is CR⁵ or N;
- A is CH, CR⁴ or N;
- n is 0, 1, 2, 3 or 4;
- 25 Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen; R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)-amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of
- 30 the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy-C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C₁₋₆alkyl)amino, aryl and Het; or
- 35 R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;
- R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-
- 40 carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalo-methyloxy, or when Y is CR⁵ then R⁴ may also represent C₁₋₆alkyl substituted with cyano or aminocarbonyl;
- 45 R⁵ is hydrogen or C₁₋₄alkyl;
- L is -X¹-R⁶ or -X²-Alk-R⁷ wherein

R⁶ and R⁷ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR⁵ then R⁶ and R⁷ may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethoxy and trihalomethyl; or when Y is N then R⁶ and R⁷ may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;

10 X¹ and X² are each independently -NR³-, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -S(=O)₂-;

15 Alk is C₁₋₄alkanediyl; or

when Y is CR⁵ then L may also be selected from C₁₋₁₀alkyl,

20 C₃₋₁₀alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, or C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, C₁₋₆alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethoxy and C₁₋₆alkylcarbonyl;

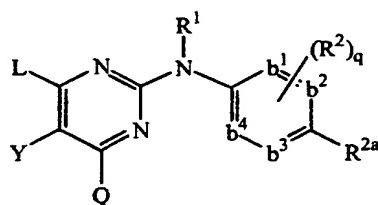
25 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro and trifluoromethyl;

30 Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

The compounds of formula (I) can be prepared according to the methods described in the patent applications with application number PCT/EP99/02043 and PCT/EP99/02044.

(II) is an antiviral compound of formula

5



(II)

10 the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

-b¹=b²-C(R^{2a})=b³-b⁴= represents a bivalent radical of formula

-CH=CH-C(R^{2a})=CH-CH= (b-1);

15

-N=CH-C(R^{2a})=CH-CH= (b-2);

-CH=N-C(R^{2a})=CH-CH= (b-3);

-N=CH-C(R^{2a})=N-CH= (b-4);

-N=CH-C(R^{2a})=CH-N= (b-5);

-CH=N-C(R^{2a})=N-CH= (b-6);

20

-N=N-C(R^{2a})=CH-CH= (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

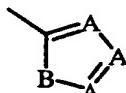
R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl;

25 R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C₁₋₆alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C₂₋₆alkenyl substituted with cyano, or C₂₋₆alkynyl substituted with cyano;

each R² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or -C(=O)R⁶, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino,

35 polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or a radical of formula

40



(c)

wherein each A independently is N, CH or CR⁶;

B is NH, O, S or NR⁶;

45

p is 1 or 2; and

R⁶ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from

* C₃₋₇cycloalkyl,

5 * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethoxy and C₁₋₆alkylcarbonyl,

10 * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or

15 L is -X-R³ wherein

R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents

20 defined in R²; and

X is -NR¹⁻, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;

Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or -NR⁴R⁵; and

25 R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxy-carbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be

30 substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H,

35 -C(=O)NHNNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or

R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄alkylidene;

Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl

40 optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H,

45 -C(=O)NHNNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;

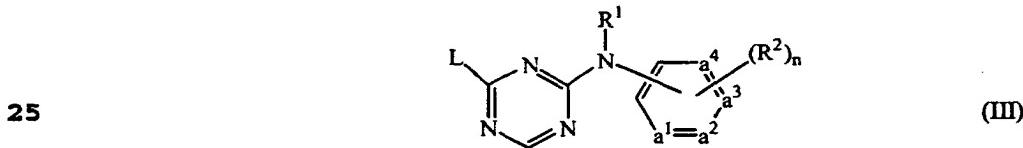
aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁-6alkyl, C₃-7cycloalkyl, C₁-6alkyloxy, cyano, nitro, poly-haloC₁-6alkyl and polyhaloC₁-6alkyloxy;

5 Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

15

The compounds of formula (II) can be prepared according to the methods described in the US patent applications with application number 60/143962 and 60/107792.

20 (III) is an antiviral compound of formula



a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, wherein
30 -a¹=a²-a³=a⁴- represents a bivalent radical of formula

- CH=CH-CH=CH- (a-1);
- N=CH-CH=CH- (a-2);
- N=CH-N=CH- (a-3);
- N=CH-CH=N- (a-4);
- 35 -N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case -a¹=a²-a³=a⁴- is (a-1), then n may also be 5;

R¹ is hydrogen, aryl, formyl, C₁-6alkylcarbonyl, C₁-6alkyl, C₁-6alkyloxycarbonyl, C₁-6alkyl substituted with formyl,

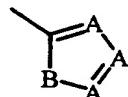
40 C₁-6alkylcarbonyl, C₁-6alkyloxycarbonyl; and each R² independently is hydroxy, halo, C₁-6alkyl optionally substituted with cyano or -C(=O)R⁴, C₃-7cycloalkyl, C₂-6alkenyl optionally substituted with one or more halogen atoms or cyano, C₂-6alkynyl optionally substituted with one or more halogen atoms or cyano, C₁-6alkyloxy, C₁-6alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁-6alkyl)amino,

45

6

polyhalomethyl, polyhalomethyloxy, polyhalomethylthio,
 $-S(=O)_pR^4$, $-NH-S(=O)_pR^4$, $-C(=O)R^4$, $-NHC(=O)H$, $-C(=O)NHNH_2$,
 $-NHC(=O)R^4$, $-C(=NH)R^4$ or a radical of formula

5



(c)

wherein each A independently is N, CH or CR⁴;

B is NH, O, S or NR⁴;

10 p is 1 or 2; and

R⁴ is methyl, amino, mono- or dimethylamino or polyhalo-
methyl;

L is C₄₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl,
whereby each of said aliphatic group may be substituted with
one or two substituents independently selected from

* C₃₋₇cycloalkyl,

* indolyl or isoindolyl, each optionally substituted with
one, two, three or four substituents each independently
selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy,

20 cyano, aminocarbonyl, nitro, amino, polyhalomethyl, poly-
halomethyloxy and C₁₋₆alkylcarbonyl,

* phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl,
wherein each of said aromatic rings may optionally be
substituted with one, two, three, four or five substi-

25 tuents each independently selected from the substituents
defined in R²; or

L is -X-R³ wherein

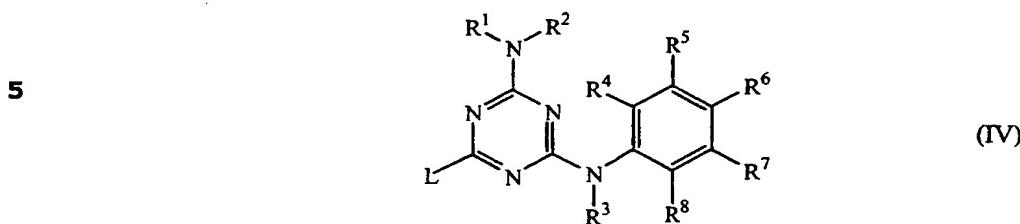
R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazi-
nyl, wherein each of said aromatic rings may optionally
30 be substituted with two, three, four or five substituents
each independently selected from the substituents defined
in R²; and

X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-,
-S(=O)- or -S(=O)₂-;

35 aryl is phenyl or phenyl substituted with one, two, three, four
or five substituents each independently selected from halo,
C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, poly-
haloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy.

40 The compounds of formula (III) can be prepared according to the
methods described in the US patent application with application
number 60/107799.

(IV) is an antiviral compound of formula



10

the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R¹ and R² are each independently selected from hydrogen; hydroxy; amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyl-oxycarbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁₋₆alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonyl-amino, hydroxy, hydroxyC₁₋₆alkyloxy, carboxyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonyl and thienyl; or R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄-alkylidene;

R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxy-carbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethoxy ; L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or L is C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indoly substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethoxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethoxy, C₁₋₆alkylcarbonyl; and,

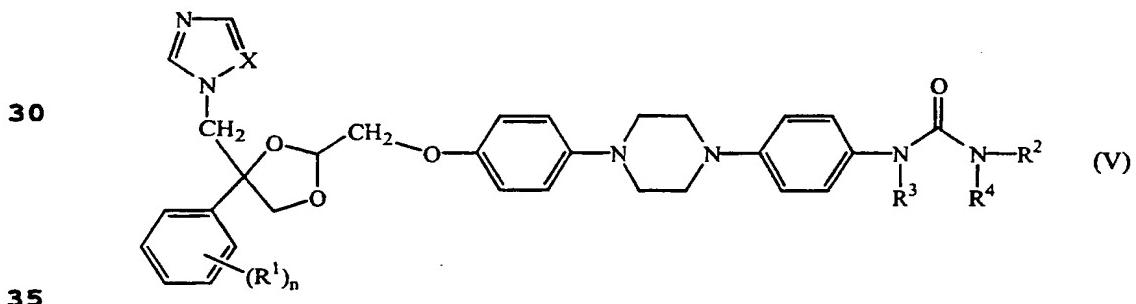
Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
5	a 1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H	H
	b 1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO ₂	H	H
	c 1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H	H
	d 1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H	H
	e 1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH ₂	H	H
	f 4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H	H
10	g 1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
	h 4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
	i 3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
	j 2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
	k 3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
	l 2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
15	m 2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
	n Phenylmethyl	H/H	H	CH ₃	H	H	H	H
	o Phenylmethyl	H/H	H	H	H	H	H	H

20 are not included.

The compounds of formula (IV) can be prepared according to the methods described in EP-A-0834507.

25 (V) is an antifungal compound of formula



the N-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein
n is zero, 1, 2 or 3;

40 X is N or CH;

each R¹ independently is halo, nitro, cyano, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl;

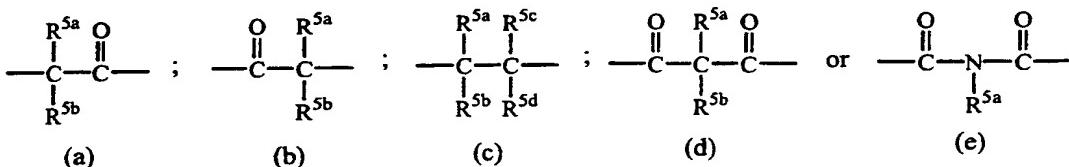
R² is hydrogen; C₃₋₇alkenyl; C₃₋₇alkynyl, aryl; C₃₋₇cycloalkyl; C₁₋₆alkyl or C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyloxy,

45 C₃₋₇cycloalkyl or aryl;

R³ and R⁴ each independently are hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl or aryl; or

R³ and R⁴ taken together form a bivalent radical -R³-R⁴- of formula:

5



10

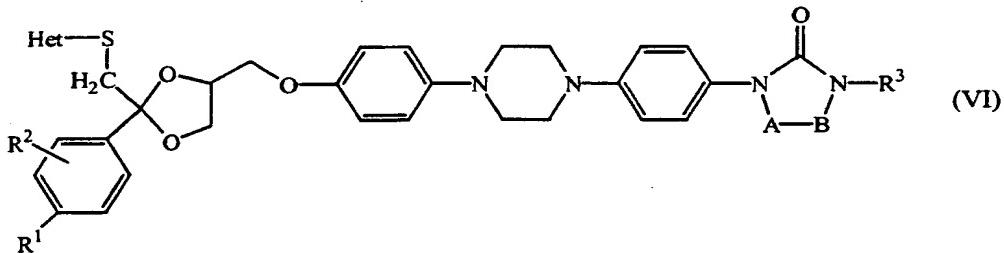
wherein R^{5a}, R^{5b}, R^{5c}, R^{5d} each independently are hydrogen, C₁₋₆alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, 15 C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl.

The compounds of formula (V) can be prepared according to the methods described in WO 99/02523.

20 (VI) is an apolipoprotein-B synthesis inhibitor of formula

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the N-oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :

35

- N=CH- (a),
- CH=N- (b),
- CH₂-CH₂- (c),
- CH=CH- (d),
- C(=O)-CH₂- (e),
- CH₂-C(=O)- (f),

40 in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C₁₋₆alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C₁₋₆alkyl;

R¹ is hydrogen, C₁₋₆alkyl or halo;

45 R² is hydrogen or halo;

R³ is hydrogen; C₁₋₈alkyl; C₃₋₆cycloalkyl; or C₁₋₈alkyl substituted with hydroxy, oxo, C₃₋₆cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino or aryl; pyrimidine; 5 pyrimidine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁₋₆alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁₋₆alkyl, 10 hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; oxadiazole substituted with one or two substituents 15 selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; thiazole; thiazole substituted with one or 20 two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; 25 aryl is phenyl or phenyl substituted with C₁₋₆alkyl or halo.

The heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom.

30 The compounds of formula (VI) can be prepared according to the methods described in WO 96/13499.

The particles comprise the compounds of formula (I) to (VI) as a solid dispersion in a polymeric matrix, wherein the poly- 35 meric matrix is consisting of a homo- or copolymer of N-vinyl-pyrrolidone. Furthermore, the invention concerns a process for manufacturing of such particles and pharmaceutical dosage forms comprising such particles.

40 The compounds of formula (I) to (VI) contained in the particles show poor bio-availability.

In order to improve the dissolution characteristics the compounds are dispersed in a polymeric matrix, preferably by using a melt- 45 extrusion process.

EP-A 0 240 964 discloses a method for producing solid pharmaceutical forms by extrusion of polymer melts which contain active substances, using as polymers homo- or copolymers of N-vinyl-pyrrolidone.

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EP-B 0 580 860 discloses a method for producing solid dispersions of drug substances in a polymeric matrix using a twin screw extruder.

- 10 It is an object of the present invention to provide rate-controlled pharmaceutical forms containing the aforementioned compounds.

We have found that this object is achieved by the particles
15 defined at the outset.

Preferred compounds according to the invention are:

4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

- 20 4-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;

4-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;

4-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-

- 25 amino]benzonitrile;

4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-amino]benzonitrile;

4-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;

- 30 4-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;

4-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

4-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-

- 35 pyrimidinyl]amino]benzonitrile;

4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]-benzonitrile;

4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]-amino]benzonitrile;

- 40 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;

1-[4-[4-[[4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone;

12

(-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[[2-(4-chlorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one,

- 5 a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

According to the present invention the term "rate-controlled" means that depending on the composition of the matrix the

- 10 particles can show instant release of the active ingredient or modified release (sustained release).

The compounds according to the invention are homogeneously dispersed in a polymer matrix consisting of a homopolymer of

- 15 N-vinylpyrrolidone or, preferably, a copolymer of N-vinyl-pyrrolidone. A preferred copolymer is a copolymer of N-vinyl-pyrrolidone and vinyl acetate, especially a copolymer obtained from 60% b.w. of NVP and 40% b.w. of vinylacetate.

- 20 The polymers show Fikentscher K values of from 17 to 90, preferably a K value of 30 (for the definition of the K value see "H. Fikentscher, Cellulose-Chemie" (1932), 58-64 and 71-74).

- 25 The polymeric matrix component is used in amounts of from 40 to 70, preferably of from 50 to 65% b.w. of the total weight of the particles.

In a preferred embodiment of the invention the polymeric matrix further comprises a surfactant, preferably a surfactant with

- 30 a HLB-value of 10-18 (HLB: Hydrophilic Lipophilic Balance). Especially preferred surfactants are selected from the group consisting of low molecular weight polyoxyethylene polyoxy-propylene block copolymers with a mean molecular weight of 1000 to 6000 g/mol, and hydrogenated castor oil which can be 35 modified with polyethylene glycol.

The amounts of surfactants used lies in the range of up to 20% b.w., preferably 5 to 15% b.w., of the particles.

- 40 In another preferred embodiment the matrix further comprises an organic carboxylic acid in amounts of up to 5% b.w. of the particles.

In another preferred embodiment of the invention the polymeric matrix further comprises hydroxypropyl methyl cellulose in 45 amounts of up to 25% b.w., preferably from 5 to 10% b.w..

The particles of the present invention are prepared as solid dispersions of the active compounds in a polymeric matrix. The term "solid dispersion" is well known in the art and means a dispersion consisting of solid components. Preferably solid dispersions are in the form of solid solutions wherein the active ingredients are molecularly dispersed in the polymeric matrix.

Such solid dispersion is preferably obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said melt and shaping of the extrudate. The melting is effected by the input of thermal and/or mechanic energy.

Depending on the composition of the matrix, the melting takes place in the range of from 40°C to 190°C, preferably 50 to 150°C. The suitable temperature range depends on the glass transition temperature of the polymer component, the properties of the active ingredients and further additives. The optimal temperature range can be established by a few simple tests.

The mixing of the active substances with the polymer and additional components of the matrix can take place before or after the melting of the polymer. Preferably the process is solvent-free which means that no additional organic solvents or water are added.

The plastification and melting preferably can take place in an extruder, a kneader or a mixing reactor, preferably in an extruder having one or more screws which may rotate in the same direction or opposite directions, especially in a twin screw extruder. The latter can be operated with or without kneading elements, but use of kneading elements is preferred because mixing is better.

The still plastic material is extruded through a die or a breaker plate and then shaped into particles. This may be effected by milling and subsequent sieving the cooled extrudate. The preferred particle size for instant release forms lies in the range of from 0.5 to 1.5 mm.

The particles, optionally together with conventional pharmaceutically acceptable excipients, may be further processed to conventional pharmaceutical dosage forms such as tablets, pastilles, suppositories, or be packed in capsules.

It is possible and particularly advantageous to produce pharmaceutical forms with rate-controlled release and improved dissolution rates of the active ingredients. This was not to be

14

expected in view of the low solubility of the active ingredients in aqueous media.

Examples**5****General method**

Powder mixes of the components were melt kneaded at 145°C for 5 min.. After cooling the solidified melts were ground and **10** sieved. The sieve fraction 0.5-1.5 mm was used for the dissolution tests.

The composition of the individual powder mixes is listed in Table 1.

15

Table 1

Example No.	1	2	3	4	5	6
Active ingredient ¹⁾	30	30	30	30	30	40
VP-VAC-copolymer ²⁾	65	55	55	60	55	47,1
Surfactant ³⁾	5	15		5	5	4,3
Citric acid				5		
HPMC					10	8,6
Surfactant ⁴⁾			15			

25 ¹⁾ 4-[[4-[2,4,6-trimethylphenyl]amino]-2-pyrimidinyl]amino]-benzonitrile

²⁾ Kollidon® VA64, VP/VAC = 60/40, BASF Aktiengesellschaft

³⁾ PEG-n-hydrogenated Castor oil

⁴⁾ polyoxyethylene polyoxypropylene blockcopolymer, mean mol.

30 weight 4000 g/mol

The dissolution tests were carried out according to USP XXIII, paddle model, pH no change test, 0.1 M HCl, at 37°C, 100 rpm

35**40****45**

15

The results are listed in Table 2.

Table 2: Dissolution Rates of particles according to examples 1-6

5

time [min]	Dissolution [%]				time [min]	Dissolution [%]	
	Ex. 1 (IR)	Ex. 2 (IR)	Ex. 3 (IR)	Ex. 4 (IR)		Ex. 5 (SR)	Ex. 6 (SR)
10	5	53	65	58	57	1	
	10	73	86	88	82	2	
	15	77	91	95	89	3	
	20	81	91	96	93	4	
15	30	87	94	99	94	6	
	60	92	93	96	94	8	96
	120	93	94	97	95		95
IR: Instant Release						SR: Sustained Release	

20 DSC-Measurements were performed with the formulations according to examples 1 to 6 in open pans (air) at temperatures of from 20 → 250°C, with a heating rate of 10°C per minute. There is no indication of crystalline drug substance in the solid dispersions.

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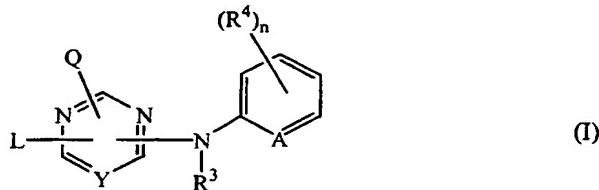
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Claims

1. Rate-controlled release particles, comprising a compound of
 5 formula I

10



a N-oxide, a pharmaceutically acceptable addition salt or a stereoisomeric form thereof, wherein

15

Y is CR⁵ or N;

A is CH, CR⁴ or N;

n is 0, 1, 2, 3 or 4;

Q is -NR¹R² or when Y is CR⁵ then Q may also be hydrogen;

20 R¹ and R² are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)-amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxy-C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, aminocarbonyl, aminocarbonylamino, mono- or di(C₁₋₆alkyl)amino, aryl and Het; or

30 R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;

35 R³ is hydrogen, aryl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyl-oxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxy-carbonyl; and

each R⁴ independently is hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyl-oxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethoxy, or when Y is CR⁵ then R⁴ may also represent C₁₋₆alkyl substituted with cyano or amino-carbonyl;

R⁵ is hydrogen or C₁₋₄alkyl;

L is -X¹-R⁶ or -X²-Alk-R⁷ wherein

45 R⁶ and R⁷ each independently are phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy,

C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyl-oxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl; or when Y is CR⁵ then R⁶ and R⁷ may also be selected from phenyl substituted with one, two, three, four or five substituents each independently selected from aminocarbonyl, trihalomethyloxy and trihalomethyl; or when Y is N then R⁶ and R⁷ may also be selected from indanyl or indolyl, each of said indanyl or indolyl may be substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, formyl, cyano, nitro, amino, and trifluoromethyl;

X¹ and X² are each independently -NR³⁻, -NH-NH-, -N=N-, -O-, -S-, -S(=O)- or -S(=O)₂-;

Alk is C₁₋₄alkanediyl; or

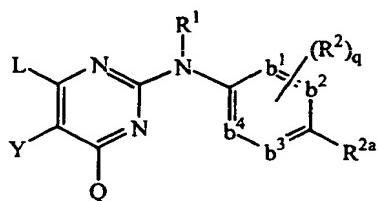
when Y is CR⁵ then L may also be selected from C₁₋₁₀alkyl, C₃₋₁₀alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, or C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl, indanyl, indolyl and phenyl, wherein said phenyl, indanyl and indolyl may be substituted with one, two, three, four or where possible five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, C₁₋₆alkyloxycarbonyl, formyl, nitro, amino, trihalomethyl, trihalomethyloxy and C₁₋₆alkylcarbonyl;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro and trifluoromethyl;

Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy.

or a compound of formula

5



(II)

10 the *N*-oxides, the pharmaceutically acceptable addition salts, quaternary amines and the stereochemically isomeric forms thereof, wherein

-b¹=b²-C(R²a)=b³-b⁴= represents a bivalent radical of formula
-CH=CH-C(R²a)=CH-CH= (b-1);

15

-N=CH-C(R²a)=CH-CH= (b-2);

-CH=N-C(R²a)=CH-CH= (b-3);

-N=CH-C(R²a)=N-CH= (b-4);

-N=CH-C(R²a)=CH-N= (b-5);

-CH=N-C(R²a)=N-CH= (b-6);

20

-N=N-C(R²a)=CH-CH= (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylicarbonyl, C₁₋₆alkyloxycarbonyl;

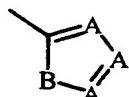
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R²a is cyano, aminocarbonyl, mono- or di(methyl)amino-carbonyl, C₁₋₆alkyl substituted with cyano, amino-carbonyl or mono- or di(methyl)aminocarbonyl, C₂₋₆alkenyl substituted with cyano, or C₂₋₆alkynyl substituted with cyano;

30

each R² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or -C(=O)R⁶, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or a radical of formula

40



(c)

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wherein each A independently is N, CH or CR⁶;

B is NH, O, S or NR⁶;

p is 1 or 2; and

R⁶ is methyl, amino, mono- or dimethylamino or polyhalomethyl;

- 5 L is C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from
- 10 * C₃₋₇cycloalkyl,
- * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethoxy and C₁₋₆alkyl-
- 15 carbonyl,
- * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or
- 20 L is -X-R³ wherein
- R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; and
- 25 X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;
- Q represents hydrogen, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl or
- 30 -NR⁴R⁵; and
- R⁴ and R⁵ are each independently selected from hydrogen, hydroxy, C₁₋₁₂alkyl, C₁₋₁₂alkyloxy, C₁₋₁₂alkylcarbonyl, C₁₋₁₂alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₁₂alkyl)amino, mono- or di(C₁₋₁₂alkyl)aminocarbonyl
- 35 wherein each of the aforementioned C₁₋₁₂alkyl groups may optionally and each individually be substituted with one or two substituents each independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, imino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁶, -C(=NH)R⁶, aryl and Het; or
- 40 R⁴ and R⁵ taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₁₂alkyl)aminoC₁₋₄-alkylidene;
- 45

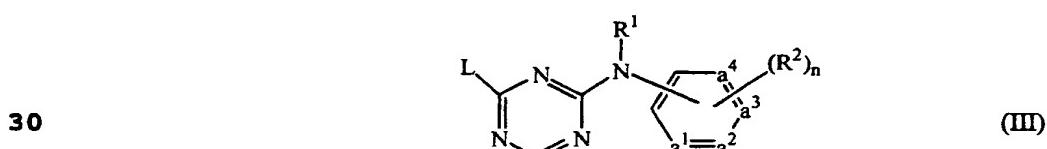
Y represents hydroxy, halo, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms, C₂₋₆alkynyl optionally substituted with one or more halogen atoms, C₁₋₆alkyl substituted with cyano or -C(=O)R⁶, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁶, -NH-S(=O)_pR⁶, -C(=O)R⁶, -NHC(=O)H, -C(=O)NNH₂, -NHC(=O)R⁶, -C(=NH)R⁶ or aryl;

5 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy;

10 Het is an aliphatic or aromatic heterocyclic radical; said aliphatic heterocyclic radical is selected from pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl and tetrahydrothienyl wherein each of said aliphatic heterocyclic radical may optionally be substituted with an oxo group; and said

15 20 aromatic heterocyclic radical is selected from pyrrolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl wherein each of said aromatic heterocyclic radical may optionally be substituted with hydroxy,

25 or a compound of formula



a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, 35 wherein

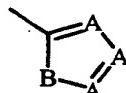
-a¹=a²-a³=a⁴- represents a bivalent radical of formula

-CH=CH-CH=CH-	(a-1);
-N=CH-CH=CH-	(a-2);
-N=CH-N=CH-	(a-3);
40 -N=CH-CH=N-	(a-4);
-N=N-CH=CH-	(a-5);

n is 0, 1, 2, 3 or 4; and in case -a¹=a²-a³=a⁴- is (a-1), then n may also be 5;

R¹ is hydrogen, aryl, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl; and

each R² independently is hydroxy, halo, C₁₋₆alkyl optionally substituted with cyano or -C(=O)R⁴, C₃₋₇cycloalkyl, C₂₋₆alkenyl optionally substituted with one or more halogen atoms or cyano, C₂₋₆alkynyl optionally substituted with one or more halogen atoms or cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethoxy, polyhalomethylthio, -S(=O)_pR⁴, -NH-S(=O)_pR⁴, -C(=O)R⁴, -NHC(=O)H, -C(=O)NHNH₂, -NHC(=O)R⁴, -C(=NH)R⁴ or a radical of formula

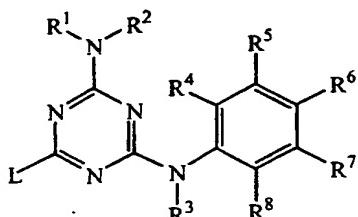


(c)

- 15 wherein each A independently is N, CH or CR⁴;
 B is NH, O, S or NR⁴;
 p is 1 or 2; and
 R⁴ is methyl, amino, mono- or dimethylamino or polyhalomethyl;
- 20 L is C₄₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, whereby each of said aliphatic group may be substituted with one or two substituents independently selected from
 * C₃₋₇cycloalkyl,
 * indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethoxy and C₁₋₆alkyl-carbonyl,
- 25 * phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R²; or
- 30 L is -X-R³ wherein
 R³ is phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with two, three, four or five substituents each independently selected from the substituents defined in R²; and
- 35 X is -NR¹-, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, -S(=O)- or -S(=O)₂-;
- 40 aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, cyano, nitro, polyhaloC₁₋₆alkyl and polyhaloC₁₋₆alkyloxy,
- 45

or a compound of formula

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(IV)

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the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

R¹ and R² are each independently selected from hydrogen; hydroxy; amino; C₁-6alkyl; C₁-6alkyloxy; C₁-6alkylcarbonyl; C₁-6alkyloxycarbonyl; Ar¹; mono- or di(C₁-6alkyl)amino; mono- or di(C₁-6alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁-6alkyl substituted with one or two substituents each independently selected from amino, imino, amino-carbonyl, aminocarbonylamino, hydroxy, hydroxyC₁-6alkyl-oxy, carboxyl, mono- or di(C₁-6alkyl)amino, C₁-6alkyloxy-carbonyl and thienyl; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁-6alkyl)aminoC₁-4-alkylidene;

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R³ is hydrogen, Ar¹, C₁-6alkylcarbonyl, C₁-6alkyl, C₁-6alkyloxy-carbonyl, C₁-6alkyl substituted with C₁-6alkyloxycarbonyl; and

R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁-6alkyl, C₁-6alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalome-thyloxy;

L is C₁-10alkyl; C₃-10alkenyl; C₃-10alkynyl; C₃-7cycloalkyl; or

L is C₁-10alkyl substituted with one or two substituents independently selected from C₃-7cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁-6alkyl, C₁-6alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalo-methyl, trihalomethyloxy, C₁-6alkylcarbonyl; phenyl or

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phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁-6alkyl, C₁-6alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁-6alkyl-carbonyl; and,

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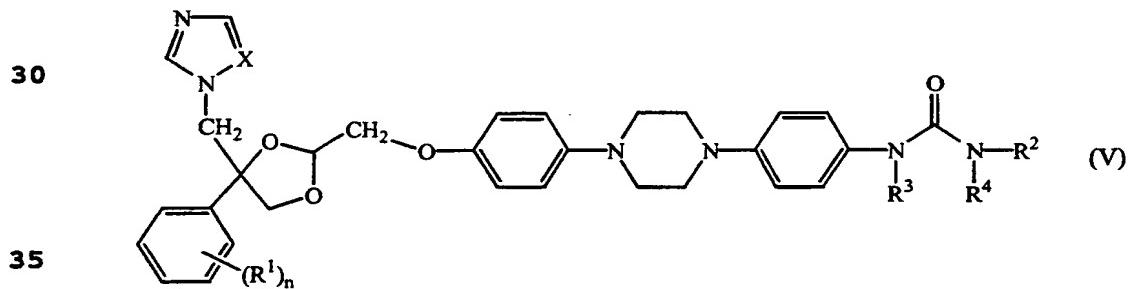
Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; with the proviso that compounds (a) to (o)

Co. No.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO ₂	H	H
c	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH ₂	H	H
f	4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H	H
g	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	H	H	H	H
m	2-(3,5-(1,1-dimethylethyl)-4-hydroxy-phenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	Phenylmethyl	H/H	H	CH ₃	H	H	H	H
o	Phenylmethyl	H/H	H	H	H	H	H	H

are not included,

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or a compound of formula



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the N-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof,

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wherein

n is zero, 1, 2 or 3;

X is N or CH;

each R¹ independently is halo, nitro, cyano, amino, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy or trifluoromethyl;

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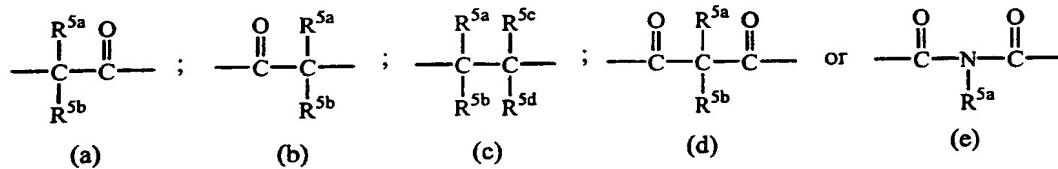
R² is hydrogen; C₃₋₇alkenyl; C₃₋₇alkynyl, aryl; C₃₋₇cycloalkyl; C₁₋₆alkyl or C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₃₋₇cycloalkyl or aryl;

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R^3 and R^4 each independently are hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or aryl; or
 R^3 and R^4 taken together form a bivalent radical $-R^3-R^4-$ of formula:

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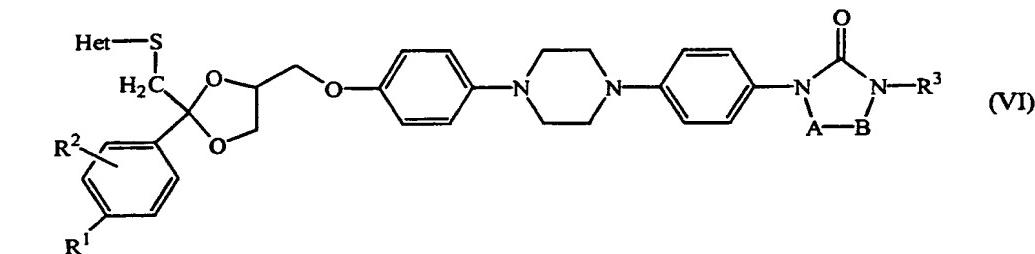
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wherein R^{5a} , R^{5b} , R^{5c} , R^{5d} each independently are hydrogen, C_{1-6} alkyl or aryl; and

aryl is phenyl or phenyl substituted with one, two or three substituents selected from halo, nitro, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxy or trifluoromethyl,

or a compound of formula



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the N -oxides, the stereochemically isomeric forms thereof, and the pharmaceutically acceptable acid addition salts, wherein A and B taken together form a bivalent radical of formula :

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- $-N=CH-$ (a),
- $-CH=N-$ (b),
- $-CH_2-CH_2-$ (c),
- $-CH=CH-$ (d),
- $-C(=O)-CH_2-$ (e),
- $-CH_2-C(=O)-$ (f),

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in the bivalent radicals of formula (a) and (b) the hydrogen atom may be replaced by C_{1-6} alkyl; in the bivalent radicals of formula (c), (d), (e), (f), one or two hydrogen atoms may be replaced by C_{1-6} alkyl;

R^1 is hydrogen, C_{1-6} alkyl or halo;

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R^2 is hydrogen or halo;

R^3 is hydrogen; C_{1-8} alkyl; C_{3-6} cycloalkyl; or C_{1-8} alkyl substituted with hydroxy, oxo, C_{3-6} cycloalkyl or aryl;

Het is a heterocycle selected from the group consisting of pyridine; pyridine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino or aryl; pyrimidine; pyrimidine substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino or aryl; tetrazole; tetrazole substituted with C₁₋₆alkyl or aryl; triazole; triazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; thiadiazole; thiadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)-amino; oxadiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; imidazole; imidazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; thiazole; thiazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino; oxazole; oxazole substituted with one or two substituents selected from C₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, trihalomethyl, amino, mono- or di(C₁₋₆alkyl)amino;

arylis phenyl or phenyl substituted with C₁₋₆alkyl or halo, and the heterocyclic radical "Het" is bound to the sulfur atom via a carbon atom,

as a solid dispersion in a polymeric matrix, wherein the polymeric matrix is consisting of a homo- or copolymer of N-vinylpyrrolidone.

35 2. Particles according to claim 1, wherein the copolymer of N-vinylpyrrolidone is a copolymer with vinyl acetate.

3. Particles according to claim 1 or 2, further comprising a surfactant.

40 4. Particles according to claim 3, wherein the surfactant is a PEG-n-hydrogenated castor oil.

5. Particles according to any of the claims 1 to 3, wherein the surfactant is a low molecular weight polyoxyethylene polyoxypropylene block copolymer.

6. Particles according to any of the claims 1 to 3, further comprising citric acid in amounts of up to 5 % b.w.
7. Particles according to any of the claims 1 to 6, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 40 to 70 % b.w. of the total weight of the dosage form.
8. Particles according to claim 7, wherein the homo- or copolymer of N-vinylpyrrolidone is used in amounts of from 50 to 65 % b.w..
9. Particles according to any of the claims 1 to 8, wherein the controlled release is an instant release of the drug.
- 15 10. Particles according to any of the claims 1 to 8, wherein the controlled release is a sustained release.
11. Particles according to claim 10, further comprising hydroxy-propyl methyl cellulose in amounts of from 5 to 10 % b.w..
- 20 12. Particles according to any of the claims 1 to 11, obtained by forming a homogeneous mixture of the components in the form of a melt, extruding said mixture and shaping of the extrudate.
- 25 13. Particles according to any of the claims 1 to 11, comprising a compound selected from the group consisting of 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]-benzonitrile;
- 30 14-[[2-[(cyanophenyl)amino]-4-pyrimidinyl]amino]-3,5-dimethyl-benzonitrile;
- 14-[[4-amino-5-chloro-6-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
- 14-[[5-chloro-4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
- 35 14-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]-amino]benzonitrile;
- 14-[[4-amino-5-chloro-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile;
- 40 14-[[5-bromo-6-[(4-cyano-2,6-dimethylphenyl)amino]-2-pyrimidinyl]-amino]benzonitrile;
- 14-[[4-amino-5-chloro-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;
- 45 14-[[4-amino-5-bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-pyrimidinyl]amino]benzonitrile;

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4-[[4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazin-2-yl]amino]benzonitrile;
4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile;
5 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile;
1-[4-[4-[4-[(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2-imidazolidinone;
10 (-)-[2S-[2alpha,4alpha(S*)]]-4-[4-[4-[4-[(2-(4-chlorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio)methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methyl-propyl)-3H-1,2,4-triazol-3-one,
15 a N-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof.

14. Pharmaceutical dosage form, comprising particles according to any of the preceding claims.
- 20 15. Pharmaceutical dosage forms according to claim 13, further comprising one or more pharmaceutically acceptable excipients.

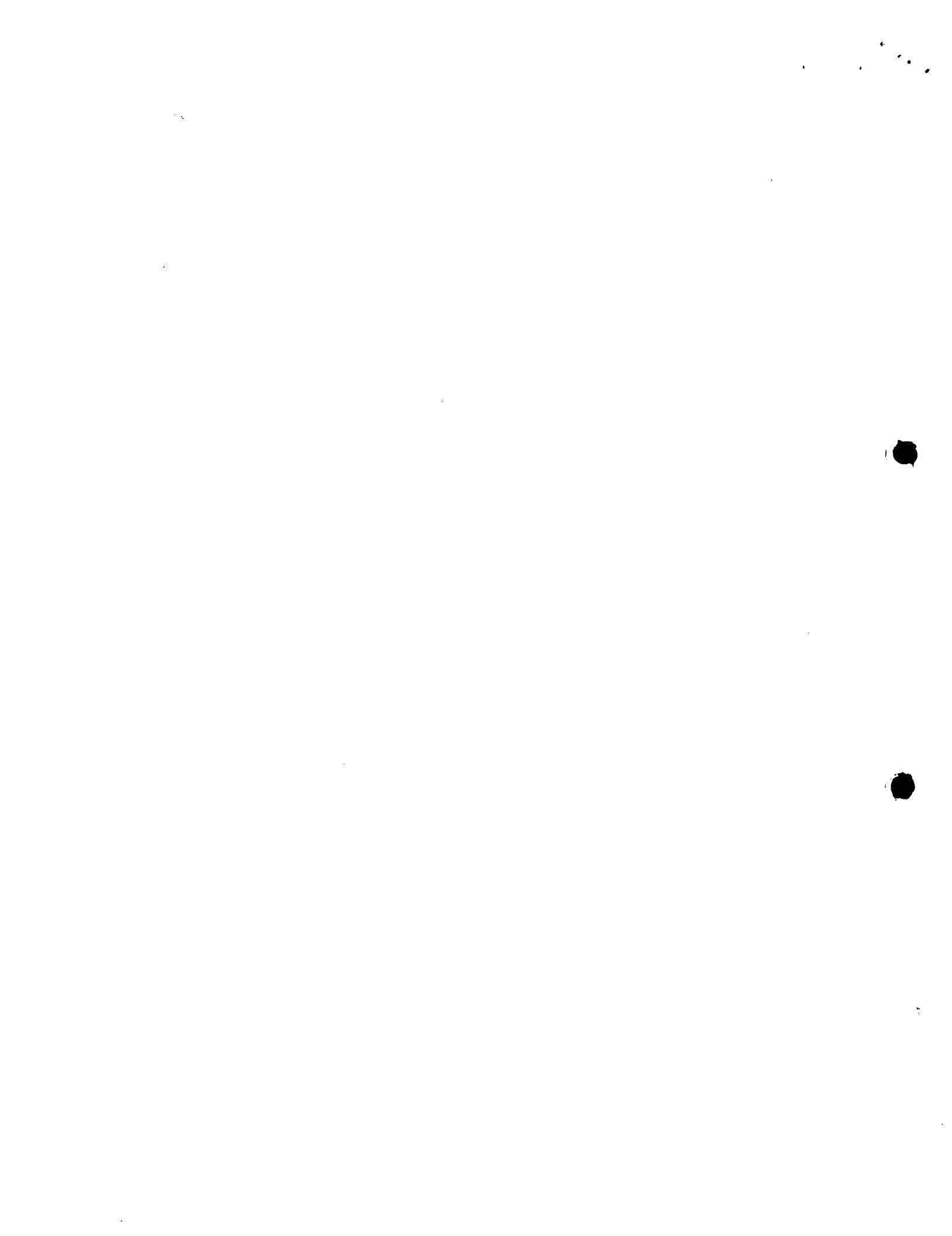
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(84) Designated States (*regional*): European patent (AT, BE,(71) Applicant (*for all designated States except US*): **KNOLL AKTIENGESELLSCHAFT [DE/DE]**; 67061 Ludwigshafen (DE).

CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,

(72) Inventors; and

NL, PT, SE).

(75) Inventors/Applicants (*for US only*): **HANTKE, Thomas** [DE/DE]; Landauerstrasse 5, 67067 Ludwigshafen (DE). **REHBOCK, Bettina** [DE/DE]; Wasgauiring 28, 67125 Dannstadt (DE). **ROSENBERG, Jörg** [DE/DE]; Bruchstrasse 29, 67158 Ellerstadt (DE). **BREITENBACH, Jörg** [DE/DE]; Hans-Sachs-Ring 95A, 68199 Mannheim (DE).**Published:**

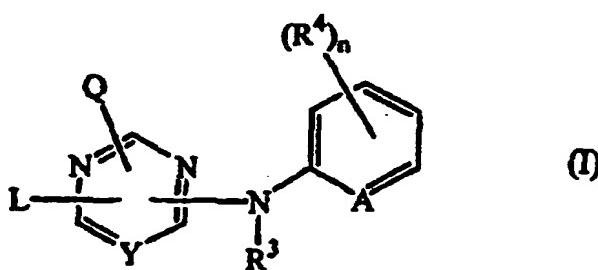
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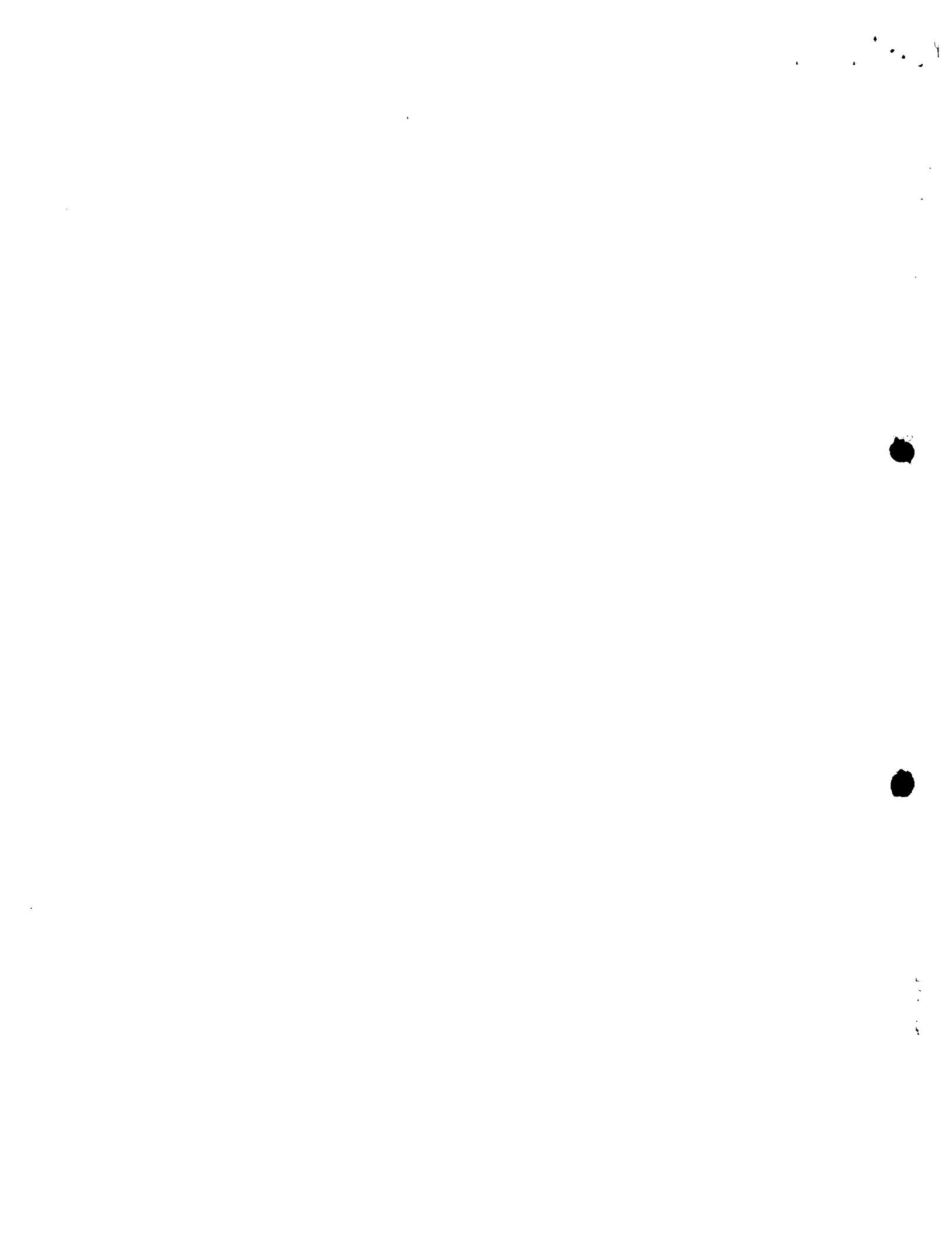
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RATE-CONTROLLED PARTICLES



(57) Abstract: Rate-controlled particles, comprising compounds of formula (I) as a solid dispersion.

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INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/EP 00/09149

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07D239/48	C07D251/18	C07D239/50	C07D403/12	C07D521/00
	C07D405/14	A61K31/505	A61P35/00	A61K9/16	A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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